# The Relationship of Intravenous Midazolam and Posttraumatic Stress Disorder Development in Burned Soldiers

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***Background:*** **Midazolam, a short-acting benzodiazepine, is administered preoperatively and intraoperatively for amnesia and anxiolysis. Subsequently, patients often do not recall events which occurred while they were sedated. Recent studies have also reported retrograde facilitation after midazolam exposure. Posttraumatic stress disorder PTSD is based on memory of a traumatic event. Because of the concern that midazolam may enhance memory of the traumatic event in which soldiers were injured, we investigated the prevalence of PTSD in those burned soldiers who received perioperative midazolam and those who did not. We also investigated the intensity of the memories related to the traumatic event.**

***Methods:*** **After institutional review board approval, all charts of US soldiers who completed the PTSD Checklist-Military (PCL-M) screening tool (2004–2008) after admission to US Army Institute of Surgical Research were reviewed to determine the number of operations, the anesthetic regime, total body surface area (TBSA) burned, and Injury Severity Score (ISS).**

***Results:*** **The PCL-M was completed by 370 burned soldiers from Operation Iraqi Freedom/Operation Enduring Freedom. During surgery, 142 received midazolam, whereas 69 did not. The prevalence of PTSD was higher in soldiers receiving midazolam as compared with those who did not (29% vs. 25%) ($p = 0.481$). Both groups had similar injuries based on TBSA and ISS. Patients who received midazolam also had similar scores on PCL-M questions related to memory of the event.**

***Conclusions:*** **Rates of PTSD are not statistically different in combat casualties receiving midazolam during intraoperative procedures. Intraoperative midazolam is not associated with increased PTSD development or with increased intensity of memory of the traumatic event. Patients receiving midazolam had similar injuries (TBSA and ISS) and underwent a similar number of operations as those not receiving midazolam.**

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Midazolam is a short-acting benzodiazepine, which causes anxiolysis, amnesia, and sedation. Midazolam exerts its effects by binding to the gamma aminobutyrate receptor ($GABA_A$) portion of the benzodiazepine binding site. When bound to the $GABA_A$ receptor, midazolam enhances binding of GABA, which causes inhibition of the central nervous system through enhanced chloride conductance. GABA is the major inhibitory neurotransmitter of the central nervous system. GABA receptors exist in the cerebral cortex, the hippocampus, the amygdala, the thalamus, the and brain stem. Activation of $GABA_A$ receptors downregulates memory formation.[1–3] The anxiolytic effects of benzodiazepines occur primarily through interactions with receptors in the amygdala and hippocampus. Benzodiazepines are used for various reasons including anxiety and stress-related disorders.

Midazolam is associated with cardiorespiratory depression and in sufficient doses may lead to respiratory compromise. It is accepted that midazolam exposure results in antegrade memory loss;[4] recently, however, Reder et al.[5] suggested a role for retrograde memory facilitation as well. After midazolam exposure, patients do not recall what they experienced while under sedation, which makes midazolam especially useful during conscious sedation for painful or unpleasant procedures. Recent work has suggested that midazolam may also increase memory of events before the sedation.[5] One hypothesis is that the reduced rate of memory formation protects recently formed memories from interference that would otherwise arise because of the demands placed on the hippocampal system.[6] Memory can be distinguished as short term or long term. Short-term memories last for seconds to minutes, whereas long-term memories last for days, weeks, years, or even a lifetime. Short-term memory becomes long-term memory by consolidation, which is the process of transforming newly learned information into stable modifications. During the initial phase of consolidation, the memory is unstable and can be disrupted by trauma, other learning, seizure, or

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administration of drugs such as protein and RNA synthesis inhibitors. Once the consolidation process is complete, memories are stable and insensitive to these interrupting factors. Established memories can become sensitive again through reactivation and can be disrupted by administration of noradrenergic blockers.[6]

Memory problems occur in combat casualties with posttraumatic stress disorder (PTSD). Up to 17% of returning Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) noninjured veterans (no combat injury) report cognitive and psychologic symptoms consistent with PTSD.[7] PTSD is a psychologic disorder characterized by recurrent flashbacks, nightmares, emotional disturbances, social withdrawal, and forgetfulness. It often arises after a traumatic experience in which the participant is threatened with harm or death. Predisposing factors for PTSD include the following: previous diagnosis of an anxiety disorder, experiencing a traumatic event, threat of injury or death, and threat to one's own physical integrity, such as untreated pain.[8,9] The risk of PTSD increases if the participant is physically harmed. This life changing disorder has been reported to affect almost half of the burn patient population with civilian burn centers reporting a range of 8% to 45%.[10–13] Recent data suggest that close to 20% of deployed service members suffer from PTSD.[14–18]

This study investigated the prevalence of PTSD in OIF/OEF service members who were treated for burns in a military treatment center to determine whether patients receiving preoperative and intraoperative midazolam had an increased prevalence of PTSD and to determine whether patients who had received midazolam had increased intensity of memories related to the traumatic event.

## PATIENTS AND METHODS

The study population included US military soldiers who had sustained any thermal injuries during OIF/OEF deployments, and who were cared for at U.S. Army Institute of Surgical Research (USAISR), and the military burn center, between 2004 and 2008. This study investigated the prevalence of PTSD in burn patients receiving preoperative and intraoperative midazolam compared with those not receiving midazolam.

Inclusion criteria for this study required that the patient have been screened for PTSD using the PTSD Checklist-Military (PCL-M) between 2004 and 2008. After institutional review board approval, medical records were reviewed to determine percent total body surface area (TBSA) burned, Injury Severity Score (ISS), total number of surgeries at USAISR within 30 days of injury, and the anesthetic regimen used, including amounts given. Thirty days post injury was chosen as a cut-off date because most patients had completed their acute phase surgery within that time. Patients were separated into groups based on whether or not they had received immediate preoperative or intraoperative midazolam.

The USAISR uses the PCL-M version as a screening tool for the assessment of PTSD in combat casualties. The PCL-M is a self-report screening tool for PTSD that is authorized for use by the U.S. military. It consists of 17 questions rated on a scale of 1 to 5 with a possible total score of 17 to 85. A score of 44 or higher yields a diagnostic efficiency of 0.900[19] so for this study a score of 44 or greater was considered as diagnostic for PTSD. The questions are designed to capture one of three distinct clusters of symptoms: reexperiencing, avoidance/numbing, or hyperarousal. The complete diagnostic criteria for PTSD are described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (1994).[9] The PCL-M was divided into individual questions. Questions 1, 2, 4, and 13 were subgrouped as to reexperiencing and nightmares.

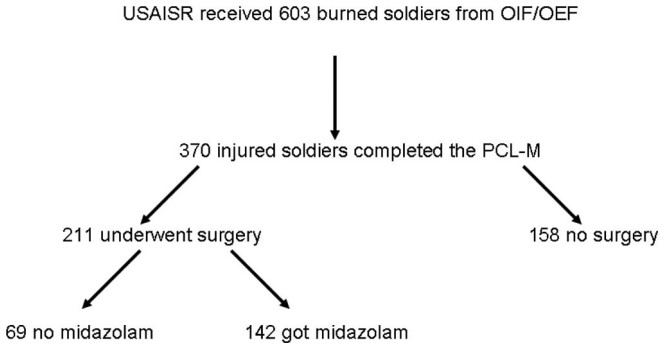


**Fig. 1.** *Schematic representation of patients receiving surgery and midazolam.*

To identify anesthetic agents used by the soldiers in the study, medical records were reviewed. Preoperative and intraoperative midazolam usage was calculated by adding the amounts in milligrams administered immediately before and during the procedure. Intraoperative ketamine usage in milligrams was calculated by adding the amount of ketamine received in the operating room. Intraoperative morphine equivalent units from the operative procedures were calculated by converting opioids (morphine, hydromorphone, fentanyl, sufenta, and methadone) into intravenous morphine equivalents by the opioid calculator at www.medcalc.com/narcotics.html.

Statistical analyses included the $\chi^2$ test on two categorical data sets, the Mann-Whitney $U$ on nonparametric data sets, the Spearman correlation test to determine the relationship between PTSD and midazolam, Logistical Regression, and receiver operated curve analysis. The null hypothesis was that rates of PTSD are not statistically different in combat casualties receiving midazolam during intraoperative procedures. Primary endpoint was the incidence of PTSD as determined by the previously validated PCL-M PTSD screening tool. Statistical significance was defined as $p < 0.05$.

## RESULTS

Of the 25,000 soldiers injured in OIF/OEF, USAISR received 370 soldiers with burns who had completed the PCL-M by the conclusion of this study. Of those, 211 soldiers underwent at least one operation at the USAISR. During surgery, 142 received midazolam and 69 did not (Fig. 1).



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The prevalence of PTSD did not change in burned soldiers receiving midazolam as compared with burned soldiers not receiving midazolam (Table 1). The prevalence of PTSD was higher in soldiers receiving midazolam compared with those who did not (29% vs. 25%), but this difference was not statistically significant as determined by the $\chi^2$test ($p = 0.481$). The demographics of the groups are listed in Table 2.

Preoperative and intraoperative midazolam usage was not associated with PTSD development. The Spearman Rank Correlation test was used to determine a correlation between midazolam and PTSD. This gave $r_s = 0.048$ ($p = 0.483$) (Table 3).

Logistical regression analysis with midazolam to predict PTSD yields a 95% confidence odds ratio interval of 0.41 to 1.522, which was not significant ($p = 0.482$). Receiver operated curve analysis with midazolam to predict PTSD gives an area under the curve of 0.618 suggesting that intraoperative midazolam usage is not a good predictor of PTSD.

**Table 1 Prevalence of PTSD in Midazolam and No Midazolam Receiving Soldiers**

| | Midazolam | No Midazolam |
|---|---|---|
| Number testing positive for PTSD | 41/142 | 17/69 |
| Prevalence of PTSD | 29% | 25% |

**Table 2 Demographics of Soldiers Receiving Midazolam or Not**

| | Midazolam (Mean ± Standard Deviation) | No Midazolam (Mean ± Standard Deviation) |
|---|---|---|
| Average TBSA | 22.6 ± 19 | 21.7 ± 19 |
| Average ISS | 18.5 ± 13 | 16.9 ± 11 |
| Average number of operations | 2.14 ± 1.6 | 1.49 ± 1.1 |
| Average morphine equivalent units per operation | 89.8 ± 66 | 94.7 ± 106 |
| Average total morphine equivalent units in OR | 226.8 ± 268 | 149.3 ± 183 |

OR, odds ratio.

**Table 3 Correlations With PTSD and Midazolam in Burned Soldiers**

| | Correlation Coefficient With PTSD | Significance |
|---|---|---|
| Midazolam | −0.048 | 0.483 |

## DISCUSSION

Patients receiving midazolam did not have an altered prevalence of PTSD. Patients receiving midazolam had similar injuries, including TBSA and ISS, and underwent similar numbers of operations. Previous data has shown that injury severity and TBSA are not associated with PTSD development in burned soldiers.[20] Civilians treated in the same U.S. military burn center display similar characteristics to military patients receiving midazolam have a similar prevalence of PTSD and similar injury characteristics (data not shown).

Burned U.S. soldiers frequently receive treatment for many years after the initial injury. They remain at the institution to receive physical therapy, plastic surgery, scar revision, and other follow-up care including being assessed for PTSD. Soldiers receiving midazolam had similar injuries to those not receiving midazolam. The midazolam receiving group has similar ISS, TBSA, underwent a similar number of operations, and received similar amounts of morphine equivalents per operation (Table 2). The minor variations between the groups were not statistically significant as determined by the Mann-Whitney *U* test.

The rates of PTSD are similar in midazolam receiving soldiers and in soldiers not receiving midazolam (Table 4). Not every patient admitted to USAISR receives surgery within the first 30 days for acute burn care. The no surgery group refers to the group of soldiers who did not receive surgery within 30 days of their injury. Thirty days was arbitrarily decided upon as the time in which most excisions acute care phase have been complete. Overall, prevalence of PTSD includes all patients assessed during that time period. The rates were numerically distinct but were not statistically distinct because of the $\beta$-error with small sample sizes. Some patients were assessed multiple times for PTSD during the course of their treatment; others were only assessed one time.

PTSD is assessed with the PCL, which is a 17-question self-report screening tool. Two versions of the PCL exist: a PCL-C (civilian) and PCL-M (military). The PCL-M is similar to the PCL-C except questions are adapted to military personnel and combat situations. A score of 44 or higher on the PCL-M is considered a positive screen for PTSD.[19] A score of 44 yields a diagnostic efficiency of 0.900, a sensi-

**Table 4 Comparison PTSD Prevalence Over Course of Time Points. Data From PCL-Ms at 1 to 3 mo, 4 to 6 mo, 7 to 9 mo, 10 to 12 mo, and More Than 1 Yr**

| | Midazolam | No Midazolam | No Surgery | Overall Prevalence of PTSD |
|---|---|---|---|---|
| Less than 1 mo | 2/7 | 2/10 | 9/53 | 13/70 (18.6%) |
| 1–3 mo | 0/0 | 5/33 | 9/36 | 14/69 (20.3%) |
| 4–6 mo | 2/17 | 10/29 | 0/1 | 12/47 (25.5%) |
| 7–9 mo | 3/11 | 8/19 | 2/11 | 13/41 (31.7%) |
| 10–12 mo | 1/5 | 5/11 | 2/4 | 8/20 (40%) |
| >1 yr | 7/18 | 5/23 | 5/8 | 17/49 (34.7%) |



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tivity of 0.944, and a specificity of 0.864, whereas the internal consistency coefficient, Cronbach's alpha, is 0.939.[19] The self-administered PCL-M and the clinician-administered PTSD screening tool have an overall correlation of 0.929.[19] The PCL assesses three areas, reexperiencing, avoiding/numbing, and hyperarousal, which correlate with the individual items on the clinician-administered PTSD Screening. All 17 items of the PCL-M have a diagnostic efficiency of 0.7 or higher.[19]

The PCL-M consists of questions to assess three symptomatic areas: avoidance/emotional numbing, reexperiencing, and hyperarousal. Four questions in the PCL-M that address the issue of nightmares and memory are questions 1, 2, 4, and 13. From the PCL-M—question 1: repeated, disturbing memories, thoughts, or images of a stressful military experience? This may occur while the soldier is awake or asleep while reexperiencing the memory. Question 2: repeated, disturbing dreams of a stressful military experience? This may occur while the soldier is asleep and reexperiencing the traumatic event. Question 4: feeling very upset when something reminded you of a stressful military experience? This may occur either during sleep or wake periods. Question 13: trouble falling or staying asleep? Sleep may be disturbed because of intrusive memories or nightmares.

Soldiers receiving preoperative and intraoperative midazolam had no significant differences in scores on questions from the PCL-M as compared with soldiers not receiving preoperative and intraoperative midazolam. Moreover, midazolam usage is not related to the scores of questions 1, 2, 4, and 13 even though they deal with reexperiencing the traumatic event (Table 5). These data suggest that administration of midazolam does not alter the intensity of memories related to traumatic event.

Recent work has suggested that midazolam may increase memory of events before the sedation.[5] Although these studies have not been duplicated, it does raise the question about how enhancement of traumatic memories may alter PTSD development in soldiers who may undergo traumatic events during combat, be transported to a treatment facility and be sedated and awake in the U.S. after 3 days of travel. Our results do not show increased memory of the traumatic event when we examine individual questions on the PCL-M.

PTSD is triggered by a specific event but does not fulfill diagnostic criteria until 30 days after the event, even though symptoms are often present shortly after the traumatic event. There is theoretically a window of opportunity to intervene between the event and the diagnosis of PTSD. Multiple prophylactic methods have been described including emotional and educational debriefing[21] and pharmacological agents.[22,23] Benzodiazepines are widely prescribed after trauma to reduce immediate anxiety because of their anxiolytic properties. However, short-term and long-term placebo controlled studies have failed to be effective.[24,25] This is similar to the results of this study where we do not see a decrease in the prevalence of PTSD after midazolam administration. Early administration of benzodiazepines has actually been associated with less favorable outcomes.[25,26]

**Table 5 PCL-M Questions From Midazolam and No Midazolam Patients**

| Question | Midazolam (Mean ± Standard Deviation) | No Midazolam |
|---|---|---|
| Repeated, disturbing memories, through or images of a stressful military experience? | 2.51 ± 1.37 | 2.59 ± 1.19 |
| Repeated, disturbing dreams of a stressful military experience? | 2.33 ± 1.32 | 2.17 ± 1.25 |
| Suddenly acting or feeling as if a stressful military experience were happening again (as if you were reliving it)? | 1.85 ± 1.16 | 1.91 ± 1.22 |
| Feeling very upset when something reminded you of a stressful military experience? | 2.38 ± 1.34 | 2.39 ± 1.21 |
| Having physical reactions (heart pounding, trouble breathing, or sweating) when something reminded you of a stressful military experience? | 2.15 ± 1.26 | 2.07 ± 1.18 |
| Avoid thinking about or talking about a stressful military experience or avoid having feelings related to it? | 2.14 ± 1.27 | 2.3 ± 1.36 |
| Avoid activities or situations because they remind you of a stressful military experience? | 2.01 ± 1.27 | 1.91 ± 1.24 |
| Trouble remembering important parts of a stressful military experience? | 2.12 ± 1.46 | 1.79 ± 1.19 |
| Loss of interest in things that you used to enjoy? | 2.14 ± 1.38 | 1.84 ± 1.26 |
| Feeling distant or cut off from other people? | 1.86 ± 1.16 | 1.94 ± 1.2 |
| Feeling emotionally numb or being unable to have loving feelings for those close to you? | 1.67 ± 1.14 | 1.71 ± 1.15 |
| Feeling as if your future will somehow be cut short? | 1.94 ± 1.35 | 1.94 ± 1.22 |
| Trouble falling or staying asleep? | 2.92 ± 1.55 | 2.87 ± 1.62 |
| Feeling irritable or having angry outbursts? | 2.45 ± 1.43 | 2.53 ± 1.34 |
| Having difficulty concentrating? | 2.27 ± 1.4 | 2.13 ± 1.32 |
| Being "super alert" or watchful on guard? | 2.38 ± 1.33 | 2.37 ± 1.3 |
| Feeling jumpy or easily startled? | 2.39 ± 1.4 | 2.37 ± 1.36 |



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The hippocampal region is frequently remodeled in response to stress and other insults. Recent evidence suggests that expression of the $GABA_A$ benzodiazepine receptor is decreased in the prefrontal cortex and hippocampal regions of PTSD patients,[23] which may explain the lack of response to benzodiazepines, including our results with midazolam.

There are several limitations to this study including the fact that this was a retrospective study with all the inherent limitations. Midazolam was dosed in accordance with individual provider preference, with intravenous doses ranging from 1 mg to 5 mg. Patients who received none were often at risk for cardiovascular collapse and hemodynamically unstable. Controls were selected from patients who completed the PCL-M and did not receive preoperative or intraoperative midazolam. Study groups were matched for demographics. Individual patients were not matched for TBSA and ISS because of the relatively small sample size. This study makes the assumption that PTSD is based on the traumatic event that resulted in the patient's burn. It does not address treatment issues, such as pain during treatment influence the development of PTSD, or their influence on the development of PTSD. Because of the military patient cohort we examined, we were not able to examine the administration of midazolam during evacuation from the current theater of conflict and transport to the burn center. Also given the frequent need for multiple or repeat operative interventions in the burn population, it is too daunting a task to consider each of the anesthetic regimens separately (i.e., total intravenous anesthesia). Likewise, aggressive extubation protocols (institutionalized attempt to lower ventilator associated pneumonia rates) frequently led to reintubation and shorter but more frequent ventilator stays.

More work remains to elucidate the contributing factors to PTSD and sequelae. Longer follow-up may be required to detect alterations in PTSD development. Although some patients were followed-up for more than 12 months, most patients were only assessed during the first 90 days after injury. This is also a relatively small sample size to detect small but significant changes in PTSD development.

Preoperative and intraoperative midazolam usage is not associated with increased PTSD development or with increased intensity of memory of the traumatic event. Patients receiving midazolam had similar injuries (TBSA and ISS) and underwent a similar number of operations as those not receiving midazolam.

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